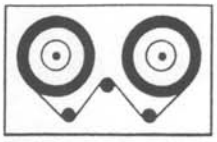
Cancer Nursing™ 20(3): 213–226, 1997.



Programmed Instruction: Human Genetics

The Genetic Basis of Cancer

Eileen Dimond, R.N., M.S., June Peters, M.S., and Jeanne Jenkins, R.N., M.S.N., Ph.D.

This is the third in a series of six self-learning modules that review the role of genetics in oncology and the implications of this information and technology for the practice of oncology nursing. This third module will review the link of genetic alterations at the cellular level to cancer initiation and development. The fourth module will review the psychosocial implications of risk assessment and of genetic susceptibility testing for cancer. The fifth module will focus on applying knowledge of cancer genetics to cancer prevention, diagnosis, and treatment, and the final module will illuminate incorporating cancer genetics into the oncology nurse's role.

OBJECTIVES

After completion of this self-learning module, the nurse will be able to do the following:

- Discuss cancer as a genetic disease.
- Define classes of cancer genes and their relationship to the process of carcinogenesis.
- Describe the relationship of genetic factors to cancer epidemiology, risk, and susceptibility.

This self-learning module has three components:

- Pretest.
- Content, with questions and answers.
- Posttest.

INSTRUCTIONS

The instructions are as follows:

- Complete the pretest.
- Read each content section and answer the questions after each section.
- Complete the posttest after completion of the self-learning module.

This module will take ~1–2 h to complete, but the module can be completed at one's own pace.

The answers to the pretest and content questions are located at the end of the module.

This module meets the requirement of the Board of Nursing, State of Florida, for Continuing Education Nursing Contact Hours Recognition as approved by the University of Florida College of Nursing Continuing Education Studies (Provider Number 27U0290).

Instructions for submission for C.N.E. credit can be found on page 226.

Eileen Dimond is a Cancer Genetics Nurse at the National Naval Medical Center, National Cancer Institute, National Institute for Health, Bethesda, MD, U.S.A.

June Peters is a Genetics Counselor at the National Human Genome Research Institute, National Institute for Health, Bethesda, MD, U.S.A.

Jeanne Jenkins is a Clinical Nurse Specialist at the National Naval Medical Center, National Cancer Institute, National Institute for Health, Bethesda, MD, U.S.A.

Address correspondence and reprint requests to Eileen Dimond, National Naval Medical Center, NCI/Navy, 8901 Wisconsin Avenue, Building 8, Room 5101, Bethesda, MD 20889-5105, U.S.A.

Accepted for publication March 27, 1997.

PRETEST:

TRUE OR FALSE:

_____ 1. Cancer may be a result of an inherited gene mutation.
_____ 2. Some cellular changes are somatic mutations.
_____ 3. Mutations that are passed on to offspring are somatic.
_____ 4. A genetic mutation is sometimes referred to as a genetic "hit."
_____ 5. Cancer is not a associated with aneuploidy.
_____ 6. A chromosomal deletion can be associated with cancer.
_____ 7. Malignant transformation may be the result of a viral insertion.
_____ 8. Tumor suppressor genes prevent malignant transformation in normal cells.
_____ 9. Disruption of apoptosis may result in cancer.
_____ 10. Understanding basic genetics is the first step in understanding cancer genetics.

THE GENETIC BASIS OF CANCER

Background

Cancer is a set of diseases in which the regulation of growth and maturity of normal cells is disturbed. There are numerous types of cancers, and even cancers of the same type can behave very differently from each other. Despite this diversity, there are fundamental changes common to all types of cancer. As Nobel Laureate and NIH Director Harold Varmus explains, "Cancer cells divide without restraint, cross boundaries they were meant to respect, and fail to display the characteristics of the cell lineage from which they were derived" (1). These changes in growth and development are under genetic control.

Cancer as a Genetic Disease

Uncontrolled cellular growth, the hallmark that distinguishes a cancerous cell from a normal one, occurs because a gene or genes that usually control this growth is/are altered in the cancer cell, resulting in dysregulated function. There are classes of genes that promote, regulate, or inhibit growth, and thus these genes are targets for malignant cellular transformation (2,3).

Types of Genetic Disorders

Although all cancer has a genetic origin at the cellular level, this does not mean all cancer is inherited. There is often confusion regarding whether a disease is *congenital, genetic, or inherited.* A condition is *congenital* when present at birth. Congenital conditions may or may not be inherited. For example, retinoblastoma or Wilms' tumor may be congenital, and each may or may not be inherited. A condition is said to be *genetic* when it involves alterations in genes. There are also > 4,000 conditions that are caused by an alteration of a single gene, thought to be *inherited* from one or both parents. Many common conditions of adulthood such as heart disease, mental illness, diabetes, and cancer have an inherited, genetic contribution in combination with other causes (4).

Several known inherited syndromes have cancer as a component, yet only a small proportion of all cancer is caused by a mutated cancer susceptibility gene inherited directly from one's parents (5,6).

Essential Properties of Normal Cells

The key processes that take place in all normal cells are cell division and cell differentiation. Cell growth and differentiation are both controlled by gene expression. Gene expression is defined by which genes are active, and which are inactive at particular moments in development. Each cell is directed by its genetic blueprint to grow and divide in an orderly progression to form the tissues and organs of the developing embryo, child, and adult. Genetic information controls the replacement of cells in the adult that have died or become old and damaged (6).

The many factors that regulate the cell cycle include specific proteins, growth factors, and environmental signals such as nutrients and temperature. Events that disrupt or damage the cell's internal regulation system, trapping it in unceasing cycles of growth, are key to development of cancer. Understanding these disruptions in the cell cycle is important in later modules during the discussion of specific genes involved in cancer causation, prevention, and treatment.

Cell Differentiation in Normal Tissue and Immaturity in Cancer Cells

Cells in one organ vary from the cells in another organ because they have become differentiated or specialized during embryonic development. Cell differentiation generally proceeds in an orderly process from immature stem cells that have the ability to divide and grow into a variety of types of cells, through intermediate, partially mature cell types, to the final specialized tissue cell that may or may not be able to divide. Like cell growth, cell differentiation is carefully regulated by the protein products of well-timed gene expression.

In contrast, cancer cells often lose or never develop the differentiated traits of the normal cells in the target organ. For example, the malignant cells in a breast tumor do not resemble the normal duct and lobule tissues of the breast, and the leukemia cells in the bone marrow fail to achieve the specialized characteristics of mature blood cells.

1. The hallmark that distinguishes a cancerous cell from a normal cell is a result of:
   _____
2. Three terms that might be applied to a child born with birth defects are:
   a. _____
   b. _____
   c. _____
3. Normal cell growth and differentiation are controlled by:
   _____
4. Cells of one organ differ from cells of another organ because:
   _____
5. Cancer cells are different from normal organ cells because:
   _____

CARCINOGENESIS

Cancer Initiation, Promotion, and Progression

Generally a tumor develops from a single cell that begins to proliferate abnormally. Cells become precancerous, then fully malignant through a series of cumulative and progressive changes at every level from the genetic code to gene expression in proteins to final clinical manifestations (phenotype) of cancer (7).

Cancer rarely occurs because of one event; rather, carcinogenesis is a multistep process resulting from the accumulation of numerous genetic mutations in the originating cell that cause uncontrolled cell growth. An example of this process in colon cancer follows.

A Model for Carcinogenesis

A model for understanding the interplay of gene mutations and the evolution from a normal to cancerous cell has been elucidated in colorectal carcinoma (8,9). The Vogelstein model illustrates the progression from a benign adenoma to metastatic colorectal cancer (Fig. 1). In this model, it is not so much the *order* of genetic events that is problematic to the DNA—rather it is the *accumulation* that warrants notice and further study. Multiple insults to the DNA have a cumulative negative effect.

Four critical gene mutations not found in normal colonic epithelia have been noted in colorectal carcinomas: the activation of the oncogene K-RAS on chromosome 12p, the loss of tumor suppressor genes DCC and p53 on chromosome 18q and 17p, respectively, and the mutation or loss of the APC gene on chromosome 5q (Fig. 1). These processes of activation and loss are the DNA changes which appear to substantially effect the cellular transformation from normal to malignant. This model is now being applied to the study of other malignancies: bladder, small cell lung cancer, astrocytomas, and breast cancers (8,9).

Cancer Invasion and Metastasis

Tumor cells relate to their surroundings in ways that differ from normal. Lacking contact inhibition, they continue moving in their own course, migrating over adjacent cells, and growing in chaotic ways. They fail to respond to signals from neighboring cells, and they send out inappropriate signals to their neighbors. For example, some cells in some tumors activate genes that produce enzymes that decompose the protein barriers that normally exist between cells. Other tumors produce angiogenesis growth factors that cause blood vessels to develop and nourish the tumor. The new blood vessels also provide an opportunity for malignant cells to be spread throughout the body via the circulatory system. These angiogenesis genes would be turned off in normal cells (3).

6. Cancer develops as a result of what three steps?
   a. _____
   b. _____
   c. _____
7. Carcinogenesis is a progressive process that proceeds due to:
   _____
8. Invasion and metastasis occurs through what three cellular processes?
   a. _____
   b. _____
   c. _____

SOMATIC (ACQUIRED) MUTATIONS VERSUS GERMLINE (INHERITED) MUTATIONS

Cellular changes that occur in cancer are often referred to as "somatic" versus "inherited." An understanding of the genetic meaning of these terms is essential when clarifying the cellular origins of cancer. Most genetic changes leading to cancer occur in isolated cells in individuals who would be considered "genetically normal." These genetic changes in an individual cell located in a specific tissue of the body are called somatic or acquired mutations. In contrast to somatic mutations, inherited mutations are those that are present in the DNA of every cell of a person's body, including the germline cells (egg and sperm).

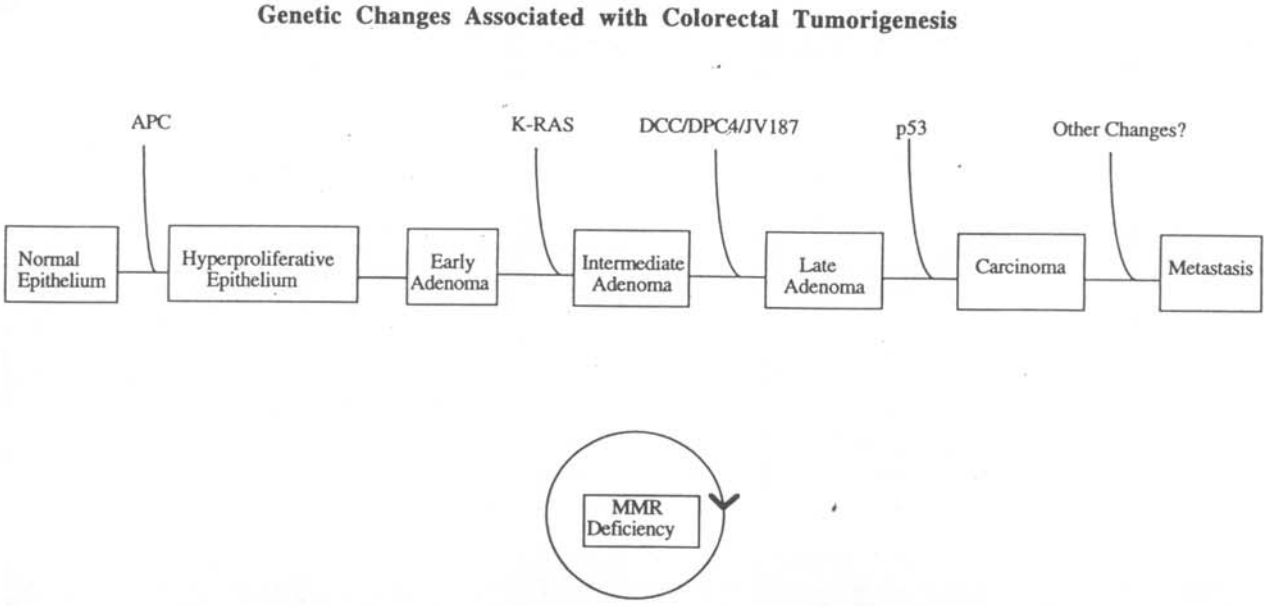


FIG. 1. An example of the multi-step process of carcinogenesis involving mutations in various oncogenes and tumor supressor genes. (From: Lessons from Hereditary Colorectal Cancer. Kinzler & Vogelstein. Copyright 1996 by Kinzler. Used with permission of Cell Press.)

Somatic Mutations

A somatic mutation is a gene alteration in an individual cell that may not be repaired and is thus replicated into all future descendants of that altered cell. Somatic cells are body cells that are not reproductive cells (10). Once the genetic change has occurred, it will be present in each of the daughter cells from the cell initially acquiring the mutation. This is said to be a genetic clone. These cloned changes are unique to the cells in that particular organ cell line and are not passed on to one's offspring because the somatic mutations are not present in the egg or sperm cells. In general, for a cell to become cancerous, it must develop more than one somatic mutation. This is especially true for the common epithelial cancers of adulthood, as exhibited in the previous colon cancer model. The need for a cell to experience multiple insults before malignant transformation provides protection to the organism. This is not necessarily the case in the embryonal cancers of early childhood discussed later.

Germline Mutations

Germ cells are the reproductive cells of the body (sperm and egg cells) (10). Germline mutations can be passed on to offspring. A person who inherits a mutation in a specific cancer susceptibility gene can develop cancer more easily, and at a younger age than a person born without such a mutation. This is especially true in the cancers of childhood, such as retinoblastoma and Wilms' tumor. Why? Because every cell already carries an inherited mutation. Therefore, every cell is already one step closer to malignant transformation (Fig. 2).

The "Two Hit" Theory of Tumor Development

The concept of inherited versus acquired cancer susceptibility is well illustrated in Dr. Knudson's "two hit" theory. In 1971, Dr. Alfred Knudson proposed a model to explain the epidemiology of retinoblastoma (Rb), a childhood cancer distinguished by retinal tumors. He suggested that more than one genetic mutation ("hit") was necessary for either inherited (positive family history) or sporadic (no family history) Rb to occur. People born with a germline Rb mutation have a DNA mutation in every cell of their bodies present at birth (the first "hit"). Any retinal cell that acquires a second "hit" in the Rb gene can develop into an Rb tumor. Therefore, people bearing a germline mutation are more likely to develop cancer than those born without this first mutation. The tumors usually occur earlier in life (e.g., infancy versus toddler), and more often present as multiple tumors versus one (because more than one cell involved in malignant transformation may have experienced the second "hit"). In addition, persons with inherited retinoblastoma are more prone to specific second primary malignancies (e.g., osteosarcomas, hepatoblastomas) (11).

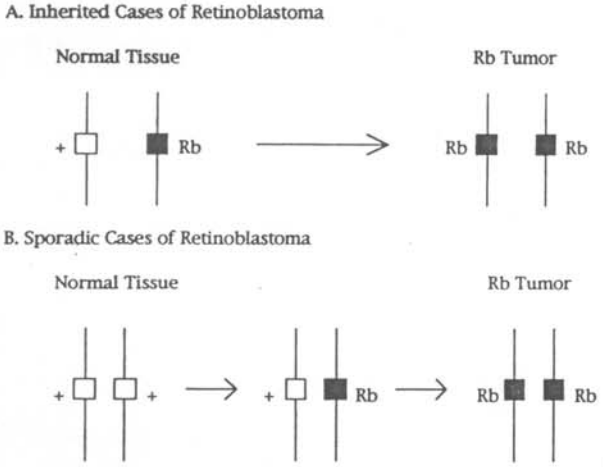


FIG. 2. Knudson's Two-Hit Model of Carcinogenesis. (A) Individuals with germline mutation of the retinoblastoma gene need only one further mutation for the eye tumor to develop. (B) In sporadic cases, two somatic mutations are needed for the evolution of a retinoblastoma. +, Normal allele; rb, Retinoblastoma gene containing germline mutation. Used with permission from Schneider K. *Counseling about cancer: strategies for genetic counselors.* Wallingford, Pennsylvania: National Society of Genetic Counselors, 1994. (As cited from: Knudson A. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A* 1971;68:820–3.)

In contrast, people born without an Rb mutation in their germline cells must acquire two mutations ("hits") in the same retinal cell to develop cancer. This noninherited form of retinoblastoma manifests as later onset disease (pediatric versus newborn), is more often unilateral, and is not as frequently associated with other cancer development (Fig. 2).

Knudson's "two hit" theory of tumor development may not apply to all cancers, but the basic concept was validated with the cloning of the Rb tumor suppressor gene. It was demonstrated that in Rb tumors, both copies of a pair of Rb genes are inactivated; thus, the "hits" necessary to transform a cell toward malignancy can be both inherited and acquired (11).

9. Cellular changes that are detected in solid tumors and hematologic cancers are often referred to as:

_____

10. Mutations that can be passed on are:

_____

11. Inherited versus acquired cancer susceptibility is explained by:

_____

GENETIC INSTABILITY: HOW GENES BECOME ALTERED TO PRODUCE CANCER

Normally, the DNA of cells incorporated into the 46 chromosomes is stable, replicating faithfully each time a cell divides into two. When damage occurs in the DNA of these somatic cells, there are generally DNA repair mechanisms to fix the problem. Thus, most cells in the body have a consistent genetic makeup (Fig. 3).

Genetic Instability in Cancer

Disruptions in DNA repair mechanisms happen naturally with aging, which is why cancers become more prevalent as we enter late adulthood. Genetic instability can also occur because of exposure to occupational and environmental carcinogens, inheritance, or chance.

Many processes that maintain the fidelity of DNA replication and repair become increasingly erratic in cancer cells. Some of these changes may help the premalignant cell to grow more rapidly, compete more effectively with normal cells for essential nutrients, relax control mechanisms of cell differentiation, and progress toward a more malignant type of cell. Mechanisms that result in genetic information changes are not mutually exclusive. Rather, the multistep process of carcinogenesis requires many cumulative genetic changes to occur over time. This frame discusses the many ways in which these can occur (8,12).

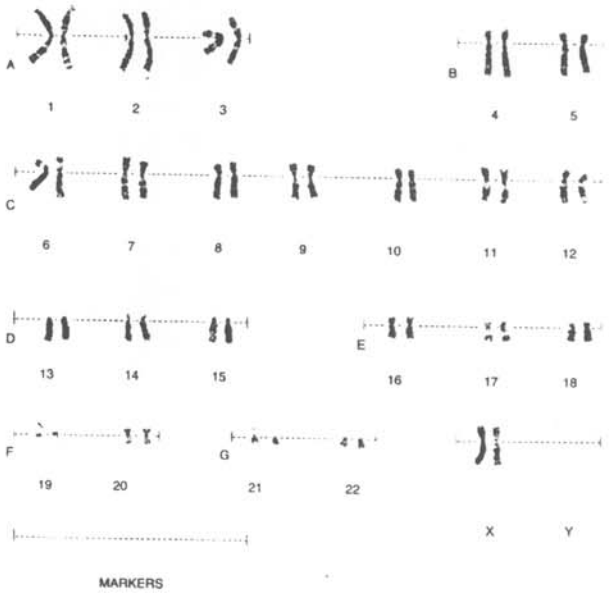


FIG. 3. A karyotype from a patient with a normal (46 XX) chromosome complement. (Used with permission of Dr. Christine Stephenson, OncoGenetics, Phoenix, AZ.)

Gene Mutations and Deletions

As described in an earlier module, the sequence of nucleotide base pairs in the DNA make up the genetic code. A mutation is a change in the ordered sequence of bases. A deletion is the elimination of one nucleotide base or a sequence of bases. These changes may be as small as a substitution of one nucleotide base for another, or as large as the deletion of a whole segment of a gene or group of genes. As reviewed in the second module of this series, DNA is transcribed into RNA. After some editing, RNA is translated into an amino acid sequence to produce the finished protein product. Thus, mutations or deletions in the DNA sequence result in an abnormal RNA sequence and ultimately an abnormal protein (4).

Chromosome Abnormalities

Many types of cancer feature an abnormal number or arrangement of chromosomes in tumor cells (7). This information often has prognostic implications. Chromosomal aneuploidies (either more or less than the normal number of 46) are manifestations of genetic instability at the largest end of the scale (Fig. 4). Aneuploidy can often be detected by diagnostic tests such as flow cytometry or cytogenetic analysis. Structural abnormalities of the chromosomes are also possible. A large segment of genetic information found on one of the chromosomes can be inverted, deleted, duplicated, or translocated to another chromosome (Fig. 5). These rearrangements can be detected through cytogenetic studies or through newer techniques that combine molecular technologies with cytogenetics, such as fluorescent in situ hybridization (FISH) (13), comparative genomic hybridization (CGH) (14,15), and spectral karyotyping (SKY) (16). These types of genetic rearrangements frequently result in the disruption of a gene, which can eventually lead to malignancy.

In leukemia, white blood cells often show rearrangements, duplications, and deletions of portions of their chromosomes. The identification of the specific chromosome rearrangement can assist with the diagnosis of a specific type of leukemia. For example, the Philadelphia chromosome, seen in chronic myelogenous leukemia, is characterized by the translocation of genetic material between chromosomes 9 and 22, leading to a genetic rearrangement in which the *abl* proto-oncogene from chromosome 9 becomes fused with the *bcr* gene from chromosome 22 (Fig. 5). The result of this translocation is the production of an abnormal combined *bcr/abl* protein that contributes to the development of leukemia.

Viruses and Cancer

Another way in which the genetic information of a normal cell can be mutated is by insertion of viral DNA. DNA viruses incorporate themselves into a host's DNA. In many cases this leads to cell death, but some infected

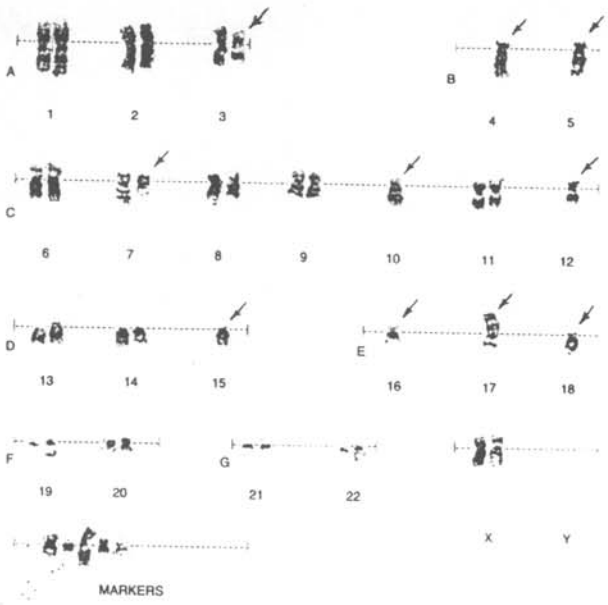


FIG. 4. A karyotype from a patient with acute nonlymphocytic leukemia (ANLL) with complex chromosomal abnormalities (additions and deletions). (Used with permission of Dr. Christine Stephenson, OncoGenetics, Phoenix, AZ.).

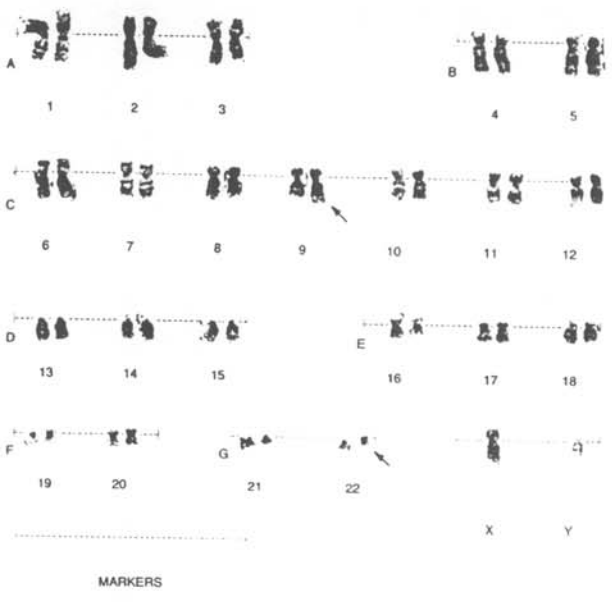


FIG. 5. A karyotype from a patient with chronic myelogenous leukemia (CML) shows a "Philadelphia chromosome" due to a translocation between chromosomes 9 and 22. (Used with permission of Dr. Christine Stephenson, OncoGenetics, Phoenix, AZ.)

cells convert to cancer cells by the introduction of viral genetic information. Examples of viral induction of cancer include the Epstein-Barr virus associated with Burkitt's lymphoma, hepatitis B virus causing liver cancer, and certain strains of human papilloma virus (HPV) contributing to cervical cancer (1).

Gene Amplification

In other cases, the "volume" of a normal gene message can be turned up. This may occur either through gene amplification or increased gene expression. Gene amplification occurs when errors in replication lead to the presence of multiple copies of an oncogene that give the cell extra messages to grow. Cells containing an amplified oncogene may thus have an advantage over surrounding cells and contribute to the aggressive growth of the malignancy. An example of this process is the amplification of the N-*myc* oncogene in some cases of neuroblastoma.

Increased Chromosomal Breakage and Defective DNA Repair

There are a variety of inherited disorders characterized by abnormalities in the mechanisms that repair chromosomal and DNA damage. These are all associated with increased risks of congenital abnormalities as well as cancer. Examples include defective DNA repair in ataxia telangiectasia and xeroderma pigmentosa, in which individuals cannot repair radiation damage to the DNA. Bloom syndrome involves a mutation in a gene that codes for a protein necessary for maintaining chromosome stability (5).

Imprinting and Cancer

Genomic imprinting is another way genetic material can be altered. It is defined as a "gamete-specific modification causing differential expression of the two alleles (variant forms of the same gene) of a gene in somatic cells" (17). In other words, some genes are chemically marked or imprinted so that they will be expressed differently, depending on whether they are inherited from the mother or the father.

Imprinting has been documented in several malignant conditions including the pediatric conditions of Wilms' tumor, bilateral retinoblastoma, embryonal rhabdosarcoma, osteosarcoma, neurofibromatosis type I, MEN 2B, and neuroblastoma. Adult cancers such as leukemias also demonstrate evidence of imprinting. For example, in the previously mentioned "Philadelphia" chromosomal translocation there is a parent-specific composition with the translocated chromosome 9 often from the father and the chromosome 22 from the mother (Fig. 5).

12. Disruption in DNA repair mechanisms can result in:

    _____

13. A change in the ordered sequence of bases of a cell's DNA is known as a:

    _____

14. Having more or less than the normal number of 46 chromosomes is known as:

    _____

15. Three examples of viral DNA insertion and cancer are:
    a. _____
    b. _____
    c. _____

16. Increased gene expression can be due to:

    _____

17. Three examples of inherited disorders that are characterized by abnormalities in the mechanisms that repair chromosomal and DNA damage are:
    a. _____
    b. _____
    c. _____

18. Gamete-specific modification of gene expression of either the maternal or paternal allele of a gene is defined as:

    _____

CLASSES OF CANCER-CAUSING GENES

Oncogenes

Oncogenes are a class of genes that play a role in the growth of cells, but when overexpressed or mutated can foster the growth of cancer (10). Oncogenes can be likened to the accelerator in a car. Their role in cancer development is that of promoting uncontrolled cellular growth. Oncogenes, in general, are inherited in a dominant fashion. This means a single alteration in one of these paired genes is sufficient to promote carcinogenesis.

Initial knowledge of oncogenes came from early studies (before 1970) that focused on cancer-causing viruses as the culprits in initiating transformation from normal

cell to tumor at the cellular level. The classic definition of an oncogene is a cancer-causing gene carried by an acute transforming retrovirus that has a normal counterpart (homologue) referred to as a proto-oncogene (18). Cancer-causing oncogenes were identified, and generally named, based on the virus in which they were originally carried. For example, SRC is an oncogene from the Rous sarcoma virus, *SIS* from the Simian sarcoma virus, *RAS* from the rat sarcoma virus, and so forth (Fig. 6) (1).

In the 1970s, it was discovered that oncogenes encode proteins involved in signal transduction. Signal transduction is "the orderly and specific transmission of growth-regulatory messages from outside the cell to the machinery controlling replication inside the cell's nucleus" (19). Discovery of the oncogene's involvement in this pathway gave clues as to how cells move from resting to proliferating and thus revealed an avenue toward understanding how tumors might be regulated. From this work came the recognition that this signal transduction pathway is a *normal mechanism* for cell growth, and thus these signal transduction genes were renamed proto-oncogenes from oncogene.

When functioning physiologically, that is, signaling growth in a normal, orderly fashion, oncogenes are termed proto-oncogenes. Mutations of the proto-oncogenes lead to a permanent activation of the pathway promoting cellular division and growth, thus leading to cancer. The mutations in the signal transduction pathway are complex, and their elucidation is the source of much investigation. A future therapeutic goal will be the interruption of these signals that drive tumor growth (19,20).

Currently, the generic term "oncogene" is problematic in that it is overused to describe any gene linked to carcinogenesis, or uncontrolled cellular growth. As described in the subsequent sections, there are specific cancer-causing genes that act via different pathways that lead to cancer and would not be appropriately described as "oncogenes" (12).

Name of Oncogene	Tumor Associations
ERB-B2, NEU	Breast, ovary, gastric
MYC	Lymphomas, carcinomas
BCL2	Lymphomas
RET	Thyroid carcinoma
Ki-RAS	Lung, Colon
Ha-RAS	Bladder
NMYC	Neuroblastoma

FIG. 6. A non-inclusive list of some currently recognized oncogenes.

Tumor Suppressor Genes (TSG)

Tumor-suppressor genes (TSGs) are genes that are present in all normal cells and function to restrain cell growth, but when missing or inactivated by a mutation, allow cells to grow in an uncontrolled manner (10). If oncogenes act like car accelerators (growth promoters), then TSGs genes are analogous to the brakes (growth inhibitors). Having one functioning copy of a TSG pair will often accomplish this job by preventing malignant transformation of a normal cell. If the second gene copy is lost, the cell is left with no working copy of that gene. This may happen due to a gene mutation or deletion. Gene deletion can occur if all or part of the chromosome the TSG is on is lost. This is referred to as loss of heterozygosity (commonly abbreviated as LOH).

In inherited cancers, one copy of a gene is mutated at birth. With inactivation of the second gene, cellular growth is no longer well controlled and cancer can occur. Consequently, people born with one altered copy of a gene pair are at a much higher risk of developing cancer because they only have one functioning gene in reserve. This is precisely what happens in the previously discussed heritable retinoblastoma (Rb).

In contrast to oncogenes that require activation, it is the *inactivation* of TSGs that leads to cancer. This is referred to as a recessive function [meaning both alleles (or copies) of the gene must be altered for function to be lost]. It is now believed that TSG inactivation contributes to many cancers (Fig. 7) (18).

Mismatch Repair Genes (MMR), Replication Errors, and Cancer

Even more recently, mutations have been shown in genes that control the accuracy of DNA replication during cell division. These genes are called mismatch repair (MMR) genes. These genes are responsible for both overseeing DNA replication and repairing any mistakes that occur during the process. "Replication errors" (RER) are an example of genetic instability that can lead to cancer. An alteration in the MMR genes prevents both the recognition and correction of DNA errors as the DNA is copied, similar to a defective spell-checking mechanism on a computer (21).

Mutations in any one of several MMR genes cause a genetic syndrome known as hereditary nonpolyposis colon cancer (HNPCC), characterized by colorectal,

Name of Tumor Suppressor Gene	Tumor Associations
DCC	Colon
APC	Colon, Familial Polyposis
BRCA1 & 2	Hereditary Breast, ovarian
p53	Leukemia, multiple carcinomas
Rb	Retinoblastoma
WT1	Wilms' Tumor

FIG. 7. A non-inclusive list of some currently recognized tumor suppressor genes.

endometrial, and other cancers. One of the hallmarks of this condition is the RER that accumulate in the tumor tissues and can be detected through special DNA studies. This genetic instability may directly cause cancer or may activate or inactivate other key genes that also participate in the carcinogenesis process.

Apoptosis (Death) Genes

Cells are programmed to age and die. This "death" pathway is called apoptosis (from the Greek word "falling off"). Disruption of this pathway may lead to cancer as cells slated to die continue to live. These "immortal cells" continue to collect DNA mutations and are thus more susceptible to malignant transformation. Follicular lymphoma is an example of cancer associated with defective apoptosis. Because of a chromosomal translocation, a gene called BCL2 is disrupted. This gene's expression is normally tightly controlled. Affected individuals inappropriately express BCL2 in B cells, thus bypassing the normal apoptotic pathway and allowing the cell a survival advantage that can lead to cancer (12).

Aging Genes: Telomerase

It is likely that control of cell aging and death is orchestrated by multiple genes and gene products. One product in particular, the enzyme telomerase, is being more closely evaluated for its role in the cellular aging and immortalization mechanism. Telomeres are the ends of chromosomes. Telomerase, an enzyme, helps maintain the telomeres. Telomerase is present in fetal development and then is not expressed in most somatic cells after birth. With each DNA replication, infinitesimally small pieces of the ends of the chromosomes are lost. Consequently, as cells age, genetic material is lost from the tips of the chromosome. The successive decrease in the size of the telomeres could be likened to a biological clock ticking off the finite number of DNA replications the cell has left before it dies.

Current evidence suggests that telomerase is reactivated in cancer cells. This prevents telomere erosion, thus allowing cell immortalization (22). Cancer cells rely on immortality to continue to proliferate and divide. Because telomerase is normally suppressed in most tissues in humans, a mutation in the telomerase gene pathway, which allows its continued expression, contributes to the causes of cancer. Thus, antitelomerase therapy may be a future focus for the treatment of cancer (12,22).

19. A cancer-causing gene carried by an acute transforming retrovirus that has a normal counterpart is referred to as an:

    _____

20. Oncogenes that signal cellular growth in a normal orderly fashion are known as:

    _____

21. Genes that are present in all normal cells and function to restrain cell growth are known as:

    _____

22. Genes that control the accuracy of DNA replication during cell division are known as:

    _____

23. Normal cellular death is known as:

    _____

24. An enzyme involved in cellular aging and immortalization is known as:

    _____

GENETIC FACTORS AND CANCER EPIDEMIOLOGY

Understanding the role that genetics plays in the development of cancer is a relatively new and evolving science. Although the focus of this module has been on specific genes linked to causing cancer, there are numerous other factors involved. Many cancers show features of multifactorial causality, in which several inherited, genetic, environmental, and personal factors interact to produce a

malignancy (Fig. 8). The significance of this interplay on the incidence of cancer is not yet fully understood. How these factors combine to become an individual's personal risk for cancer will be explored in the next module on risk assessment and genetic testing (23).

25. Mutifactorial causality of cancer may be due to:

CONCLUSION

The science of cancer genetics is evolving at a rapid pace. The challenge to oncology nurses, and all nurses in practice, is to first grasp an understanding of the principles of basic genetics and then to apply those principles to oncology. Although much has been learned during the past 25 years, much remains to be understood. As the complexities of cancer genetics are revealed, it will be the nurse's challenge to stay informed about the application of this science to his/her practice. Subsequent modules will begin to explore current applications of genetic technology and ideas for the future.

26. The first step to understanding cancer genetics is to understand the principles of:

GENE - ENVIRONMENT INTERACTIONS

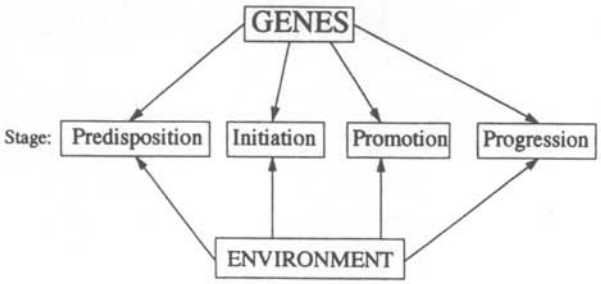


FIG. 8. Gene-environment interactions.

Acknowledgment: The authors thank our colleagues Drs. Ilan Kirsch and Liam Grogan, Betsy Glaser, and Sherry Higgins for their thoughtful review of this article, and Leslie Wheelock for her contributions to the test's questions and manuscript.

REFERENCES

1. Varmus H, Weinberg RA. *Genes and the biology of cancer.* New York: Scientific American Library, 1993.
2. Cooper GM. *Elements of human cancer.* Boston: Jones and Bartlett, 1992.
3. Cooper GM. *The cancer book: a guide to understanding the causes, prevention, and treatment of cancer.* Boston: Jones and Bartlett, 1993.
4. McKusick V. *Mendelian inheritance in man.* 11th ed. Baltimore, MD: Johns Hopkins University Press, 1997.
5. Schneider K. *Counseling about cancer: strategies for genetic counselors.* Wallingford, Pennsylvania: National Society of Genetic Counselors, 1994.
6. Hodgson S, Maher ER. *A practical guide to human cancer genetics.* Cambridge, England: Cambridge University Press, 1993.
7. Institute of Medicine. *Advances in understanding genetic changes in cancer impact on diagnosis and treatment decisions in the 1990s.* Washington, DC: National Academy Press, 1992.
8. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990;61:759–67.
9. Kinzler K, Vogelstein B. Lessons from hereditary colorectal cancer. *Cell* 1996;87:159–70.
10. *Understanding gene testing.* Bethesda: National Institutes of Health, Publication no. 96-3905, December 1995.
11. Knudson A. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A* 1971;68:820–3.
12. Kirsch I. Oncogenesis. In: Oldham KT, Foglia RB, Colombani PM, eds. *Surgery of infants and children: scientific principles and practice.* Lippincott–Raven: Philadelphia, 1996:549–67.
13. Wolman SR. Applications of fluorescent in situ hybridization (FISH) to genetic analysis of human tumors. *Pathol Annu* 1995;30:277–43.
14. Kallioniemi OP, Kallioniemi A, Sudar D, et al. Comparative genomic hybridization: A rapid new method for detecting and mapping DNA amplification in tumors. *Semin Cancer Biol* 1993;4:41–6.
15. Kallioniemi OP. Linking chromosomal clues. *Nature Genet* 1997;15:5–6.
16. Schrock E, du Manoir S, Veldman T, et al. Multicolor spectral karyotyping of human chromosomes. *Science* 1996;273:494–7.
17. Feinberg AP. Genomic imprinting and gene activation in cancer. *Nature Genet* 1993;6:273–81.
18. Weinberg R. Oncogenes and tumor suppressor genes. *CA Cancer J Clin* 1994;44:160–70.
19. Krontiris TG. Oncogenes. *N Engl J Med* 1995;333:303–6.
20. Mastrangelo MJ, Berd D, Nathan F, Lattime EC. Gene therapy for human cancer: An essay for clinicians. *Semin Oncol* 1996;23:4–21.
21. Modrich P. Mismatch repair, genetic stability and cancer. *Science* 1994;266:1959–60.
22. Shay JW, Wright WE. Telomerase activity in human cancer. *Curr Opin Oncol* 1996;8:66–71.
23. Peters JA. Breast cancer genetics: relevance to oncology practice. *Cancer Control* 1995;2:195–208.

Programmed Instruction: Answers

PRETEST

1. True
2. True
3. False
4. True
5. False
6. True
7. True
8. True
9. True
10. True

CONTENT QUESTIONS

1. Uncontrolled cellular growth occurs because a gene or genes that usually control growth are altered.
2.
   a. Congenital
   b. Genetic
   c. Inherited
3. Gene expression
4. Cellular differentiation and specialization that occurs during embryonic development.
5. Cancer cells often lose or never develop the differentiated traits of the normal cells in an organ.
6.
   a. Initiation
   b. Promotion
   c. Progression
7. Accumulation of DNA alterations
8.
   a. Lack of cellular contact inhibition
   b. Production of enzymes that decompose protein barriers between cells
   c. Angiogenesis growth factors
9. Somatic
10. Germline mutations
11. Knudson's Two Hit Theory
12. Genetic instability associated with cancer
13. Mutation
14. Chromosomal aneuploidy
15.
   a. Epstein-Barr virus and Burkitt's lymphoma
   b. Hepatitis B virus and liver cancer
   c. Human papilloma virus and cervical cancer
16. Gene amplification
17.
   a. Ataxia telangiectasia
   b. Xeroderma pigmentosa
   c. Bloom syndrome
18. Genomic imprinting
19. Oncogene
20. Proto-oncogenes
21. Tumor suppressor genes
22. Mismatch repair genes
23. Apoptosis
24. Telomerase
25. Several inherited, genetic, environmental and personal factors interact to produce a malignancy.
26. Basic genetics

POSTTEST

THE GENETIC BASIS OF CANCER

Answer the following statements True or False.

_____ 1. The need for multiple insults before malignant transformation provides protection to an organism.
_____ 2. Somatic cells are all body cells that are not reproductive cells.
_____ 3. People with a germline mutation are more likely to develop cancer than those without a germline mutation.
_____ 4. In the "Two Hit" Theory, "Hits" are only acquired.
_____ 5. Cancer cells are genetically stable.
_____ 6. All cancer cells have a normal number of chromosomes.
_____ 7. Some leukemias can be diagnosed based on a specific chromosome rearrangement.
_____ 8. Some oncogenes are involved in signal transduction.
_____ 9. Cancer can develop as a result of a proto-oncogene mutation.
_____10. Activation of tumor suppressor genes allow malignant transformation of a normal cell.

Match the following words.

11. Ki-RAS	a. Oncogene
12. BRCA 1	b. Tumor suppressor gene
13. p-53	c. Apoptosis
14. Cell death	d. Replication error
15. Mismatch repair gene	e. Telomerase
16. Immortalization	

Choose the best response for the following multiple choice questions.

17. Classes of genes that are targets for malignant cell transformation act by:
    a. promoting growth
    b. regulating growth
    c. inhibiting growth
    d. all of the above
18. At the cellular level, cell growth and differentia tion is controlled by:
    a. congenital conditions
    b. gene expression
    c. homeostasis
    d. none of the above
    e. b and c
19. Critical gene mutation(s) of colorectal cancer is/are:
    a. K-RAS
    b. DCC
    c. p53
    d. APC
    e. all of the above
    f. none of the above
    g. a and c only
20. The model that most often accounts for colorectal carcinogenesis is:
    a. gene mutation model
    b. Vogelstein model
    c. cumulative negative effect model
    d. Knudson model
    e. none of the above
21. Cellular changes in cancer cells occur by:
    a. somatic mutation
    b. acquired mutation
    c. genetic changes in cells of a specific body tissue
    d. inherited mutation
    e. all of the above
    f. none of the above
22. A gene alteration in an individual cell that may not be repaired and is then replicated into all future generations of that cell is known as:
    a. inherited mutation
    b. germline mutation
    c. congenital mutation
    d. somatic mutation
23. Mutations that can be passed onto offspring are:
    a. somatic mutations
    b. germline mutations
    c. inherited mutations
    d. b and c only
24. The "Two Hit" Cancer Theory explains:
    a. retinoblastoma
    b. inherited versus acquired cancer susceptibility
    c. model of carcinogenesis
    d. none of the above
    e. a and b only
25. In the "Two Hit" Cancer Theory, a "hit" is defined as a:
    a. gene
    b. genetic mutation
    c. cell
    d. radiation exposure

26. Forms of chromosome abnormalities that can exist in cancer cells are:
    a. aneuploidy
    b. structural changes
    c. rearrangements
    d. duplications
    e. deletions
    f. b, c, d, and e only
    g. all of the above
27. Transformation of a normal cell into a cancer cell can be the result of:
    a. chromosome abnormalities
    b. insertion of viral DNA
    c. gene amplification
    d. abnormal mechanism in repair of chromosomal and DNA damage
    e. imprinting
    f. all of the above
    g. a and b only
28. Oncogenes are involved in:
    a. signal transduction
    b. normal mechanism of cell growth
    c. none of the above
    d. a and b
29. Tumor suppressor genes are involved in:
    a. restraining cell growth in normal cells
    b. preventing malignant transformation in normal cells
    c. uncontrolled cell growth when mutated
    d. all of the above
    e. a and b only
30. Replication errors are a result of:
    a. defective mismatch repair genes
    b. translocation
    d. congenital syndromes
    e. none of the above
31. Cancer may be a result of:
    a. disruption of apoptosis
    b. replication errors
    c. reactivation of telomerase
    d. inactivation of tumor suppressor genes
    e. mutation of proto-oncogenes
    f. all of the above
    g. b and e only

Continuing Education Credit: The Genetic Basis of Cancer

Upon successful completion of the Continuing Education Posttest that accompanies this issue, 1.5 contact hours will be awarded by the University of Florida College of Nursing Continuing Education Studies, Provider Number 27U0290, Board of Nursing, State of Florida.

INSTRUCTIONS

To earn contact hours, read the materials in this issue carefully and record your answers on the Registration Form below. You must attain a passing score of at least 80% on the quiz to receive credit.

Copy or clip out this page, fill out the requested information, and mail to the address below. If you do not have a personal subscription to **Cancer Nursing™**, please enclose $10.00 for processing your test. Processing fees are waived for **Cancer Nursing™** subscribers. Failure to enclose payment may delay reporting of your credits.

The answer and registration form for this test must be received by June 30, 1998.

A continuing education certificate will be mailed to you on successful completion of the posttest.

The number of credits earned by independent study may vary with each state board of nursing. Please check with your state board of nursing regarding independent study credits.

INSERT YOUR ANSWERS FOR THE GENETIC BASIS OF CANCER

Indicate correct answer

1.	T	F
2.	T	F
3.	T	F
4.	T	F
5.	T	F
6.	T	F
7.	T	F
8.	T	F
9.	T	F
10.	T	F

List the correct answer

11. _____	18. _____	25. _____
12. _____	19. _____	26. _____
13. _____	20. _____	27. _____
14. _____	21. _____	28. _____
15. _____	22. _____	29. _____
16. _____	23. _____	30. _____
17. _____	24. _____	31. _____

This form must be filled out completely for you to receive proper credit. Please type clearly:

Name _____
Street _____
City _____ State _____ Zip _____
Phone _____ Soc. Sec. No. _____

Check one: ☐ RN ☐ LVN/LPN

Area of Clinical Practice: _____

If you are not a personal subscriber to **Cancer Nursing™**, the processing fee for each test is $10.00. Failure to enclose payment may delay reporting of your credits. Please indicate your payment method here:

☐ I am a **Cancer Nursing™** subscriber. Please waive my processing fee.
☐ Enclosed is my check for $10.00 (U.S. currency please; please make payable to Lippincott–Raven Publishers).
☐ Please charge my: ☐ Visa ☐ Amex ☐ MasterCard
Card # _____ Expires _____
Signature _____

Please mail this form to:
Sandy Kasko
Lippincott–Raven Publishers
227 E. Washington Sq.
Philadelphia, PA 19106-3780, U.S.A.

Please evaluate the Programmed Instruction by *circling the appropriate answer:* 1 = Poor, 2 = Fair, 3 = Average, 4 = Good, 5 = Excellent.

I.	How well were you able to meet the Programmed Instruction stated objectives?					
	• Discuss cancer as a genetic disease.	1	2	3	4	5
	• Define classes of cancer genes and their relationship to the process of carcinogenesis.	1	2	3	4	5
	• Describe the relationship of genetic factors to cancer epidemiology, risk, and susceptibility.	1	2	3	4	5
II.	Was the content relevant to the objectives?	1	2	3	4	5
III.	Did this method of presentation facilitate your learning?	1	2	3	4	5
IV.	Was the content appropriate to your area of practice?	1	2	3	4	5
V.	Did the content contribute to meeting your personal learning objectives?	1	2	3	4	5

Length of time taken to review the study guide (circle one)
1 h 1.5 h 2 h 2.5 h 3 h